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SEKIYAMA TAKAAKI
YATAGAI MASANORI

(54) NEW OXAZEPINE DERIVATIVE CRYSTAL

(57)Abstract:

PROBLEM TO BE SOLVED: To provide a method for industrially advantageously producing optically active 5,11-dihydro-5-[1-(4-methoxyphenetyl)-2-pyrrolidinylmethyl]dibenzo[b, e][1,4] oxazepine.

SOLUTION: A mixture of an optically active 5,11-dihydro-5-[1-(4- methoxyphenetyl)-2-phrrolidinylmethyl]dibenzo[b,e][1,4]-oxazepine with an optically active 5,11-dihydro-5-[1-[2-(4-methoxyphenyl)ethyl]piperidin-3- yl]dibenzo[b,e][1,4]oxazepine is dissolved in a solvent and nitric acid is added thereto and the deposited crystal is separated.

LEGAL STATUS

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[Date of final disposal for application]

[Patent number]

[Date of registration]

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* NOTICES *

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CLAIMS

[Claim(s)]
[Claim 1] 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate.
[Claim 2] The oxazepine nitrate according to claim 1 the 2nd place of whose of a pyrrolidine is R bodies.
[Claim 3] 5 11-hydrodibenzo [b, e] [1, 4] oxazepine And optical activity 3-chloro-1- (4-methoxy phenethyl) A piperidine Optical activity 5 which is made to react and is obtained, 11-dihydro-5-[1- Into the mixture of [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and [b, e], and 5 and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine, a solvent In addition, add a nitric acid and crystallization of the 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate is carried out. The purification approach of [b, e], and 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine characterized by dissociating.
[Claim 4] The number of optical activity 3-chloro-1-(4-methoxy phenethyl) piperidines is S. Optical activity 5 obtained at a reaction, 11-dihydro-5-[1- [b, e], and [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and optical activity 5, and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine (R) - (+) -5, 11-dihydro-5-[1- It is [b, e], and [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and (S)-5, and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine. The purification approach according to claim 3 that the nitrate which carries out crystallization is a (R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate.
[0001]

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TECHNICAL FIELD

[Field of the Invention] this invention -- calcium channel antagonism -- having -- 5 [useful to the therapy or preventive treatment of an intestinal disease such as enterokinesis dysfunction, especially irritable colon syndrome,], and the manufacture approach of a 11-hydrodibenzo [b, e] [1, 4] oxazepine derivative -- it is related with the purification approach of [b, e], and 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine in more detail.

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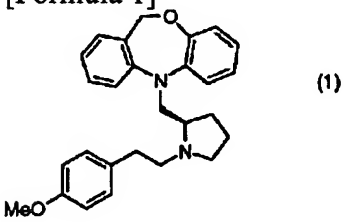
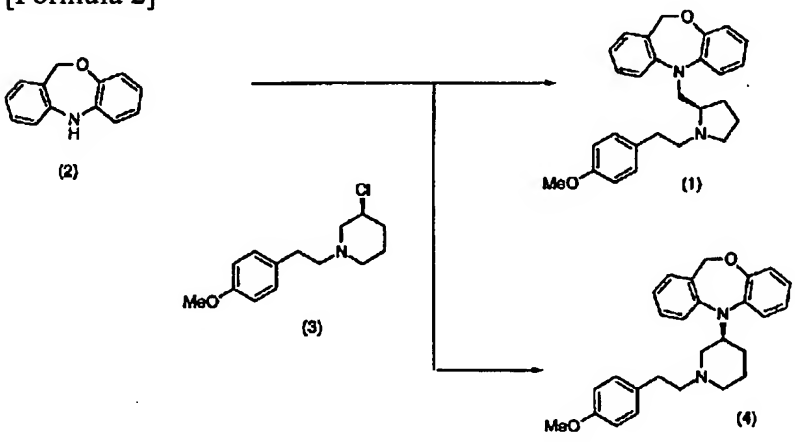
PRIOR ART

[Description of the Prior Art] [b, e], and (R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] the oxazepine shown by the following formula (1) has calcium channel antagonism, and it is known that it is useful to an intestinal disease therapy or preventive treatment, such as enterokinesis dysfunction, especially irritable colon syndrome, (WO 97/33885).
[0004]
[Formula 1]



(1)

[0005] Although the following root is shown in the above-mentioned official report as the synthetic approach of [b, e], and (R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine (1) When a (S)-(+)-3-chloro-1-(4-methoxy phenethyl) piperidine (3) is made to react to 5 of raw material, 11-hydrodibenzo [b, e], and [1, 4] oxazepine (2) In addition to the compound of the target formula (1), [b, e], and (S)-5 and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] the oxazepine which is a by-product (4) generates in large quantities. In order to obtain the target compound, the complicated purification approach needed to be used industrially [a column chromatography etc.].
[0006]
[Formula 2]



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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] It is that [b, e], and 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine establishes the useful manufacture approach industrially.

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MEANS

[Means for Solving the Problem] As a result of inquiring wholeheartedly that the above-mentioned trouble should be solved, this invention persons 5, 11-hydrodibenzo [b, e], and [1, 4] oxazepine (2) and an optical activity 3-chloro-1-(4-methoxy phenethyl) piperidine, To for example, the residue of the shape of oil acquired by carrying out extract concentration by the organic solvent, the reaction mixture of a (S)-(+)-3-chloro-1-(4-methoxy phenethyl) piperidine (3) Add a solvent, remelt this and the crystal which deposits by adding a nitric acid further is filtered. By drying, it finds out that the nitrate of [b, e], and 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine made into the purpose is obtained, and came to complete this invention.
[0009] That is, this invention is a 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate especially (R)-(+)-5, and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate.
[0010] moreover This invention 5 11-hydrodibenzo [b, e] [1, 4] oxazepine (2) And optical activity 3-chloro-1- (4-methoxy phenethyl) A piperidine Optical activity 5 which is made to react and is obtained, 11-dihydro-5-[1- Into the mixture of [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and [b, e], and 5 and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine, a solvent In addition, add a nitric acid and crystallization of the 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate is carried out. The purification approach of [b, e], and 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine characterized by dissociating. The number of especially optical activity 3-chloro-1-(4-methoxy phenethyl) piperidines is S. Optical activity 5 obtained at a reaction, 11-dihydro-5-[1- [b, e], and [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and optical activity 5, and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine (R) - (+) -5, 11-dihydro-5-[1- It is [b, e], and [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and (S)-5, and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine. The nitrate which carries out crystallization is the purification approach which is a (R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate.
[0011]
[Embodiment of the Invention] [b, e], and 5 in this invention, and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine, Especially (R) - (+) -5, 11-dihydro-5-[1- [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine (1) and [b, e], and 5 and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine, Especially the mixture of [b, e], and (S)-5 and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine (4) can be manufactured by the approach of a publication to WO 97/33885. Usually, the ratios of the compound (4) which is target compound (1) and by-product are 6:1-8:1.
[0012] In order to obtain the target nitrate, to the reaction mixture obtained by the above-mentioned approach Ethyl acetate, Extract solvents, such as toluene, dichloromethane, and isopropyl acetate, are

added. It dries with anhydrous sodium sulfate after washing if needed with water, saturation brine, etc. By condensing Optical activity 5, 11-dihydro-5-[1- [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and optical activity 5, 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [b, e] [1, The mixture of 4] oxazepine can be obtained as an oil-like residue. Since it is impossible to carry out crystallization separation of the [b, e], and optical activity 5 made into purpose from this mixture and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine independently, the next actuation refines. That is, solvents, such as a methanol, ethanol, a 2-propanol, an acetonitrile, and an acetone, are added to the residue of the shape of oil acquired above, and an oil-like residue is dissolved in it. the case where it carries out at 20-25 degrees C although the concentration at the time of the dissolution is based also on temperature -- 0.1 - 30wt% -- desirable -- 1 - 10wt% -- it is especially preferably [3 - 5wt% of] good. Although the temperature which adds a nitric acid although the target nitrate is deposited by adding a nitric acid to this solution is based also on the boiling point of the solvent to be used, it is good to carry [20-60-degree C] out at 30-50 degrees C preferably. Moreover, the concentration of the nitric acid to add is 0.4 to 0.6 convention preferably 0.25 to 1 ****. After adding a nitric acid, the target crystal can be obtained by leaving it from 6 hours at a room temperature (20-25 degrees C) for 24 hours. In this case, even if it performs churning etc., it does not interfere at all. the depositing crystal -- the usual separation approach, for example, filtration, -- shaking off -- etc. -- the target crystal can be isolated by carrying out. Usually, the purity of the target compound can be raised by washing with the solvent used for crystallization, and the partially aromatic solvent of water. Furthermore, the target nitrate can be obtained by drying this crystal.

[0013] Suspend the obtained nitrate in extract solvents, such as ethyl acetate, and alkali water solutions, such as a sodium-hydroxide water solution, neutralize it. By saturation brine's washing an organic layer after a slice, condensing if needed, and dropping a hydrogen chloride / ethyl-acetate solution at this The actually used 5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine hydrochloride can be obtained.

[0014] In addition, as mentioned above, although the researchers of this invention first tried crystallization of [b, e], and (R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine (1) made into the purpose using various solvents, neither of the solvents was able to deposit the crystal.

[0015] Moreover, although generation of the salt about acids other than a nitric acid, for example, an acetic acid, a formic acid, DL-tartaric acid, a maleic acid, a fumaric acid, a succinic acid, an adipic acid, p-toluenesulfonic acid, methansulfonic acid, a camphor sulfonic acid, and a sulfuric acid was tried, and all acquired the target salt, it was not able to do.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
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[0003]
[Description of the Prior Art] [b, e], and (R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] the oxazepine shown by the following formula (1) has calcium channel antagonism, and it is known that it is useful to an intestinal disease therapy or preventive treatment, such as enterokinesis dysfunction, especially irritable colon syndrome, (WO 97/33885).
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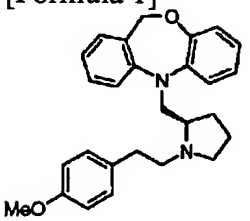

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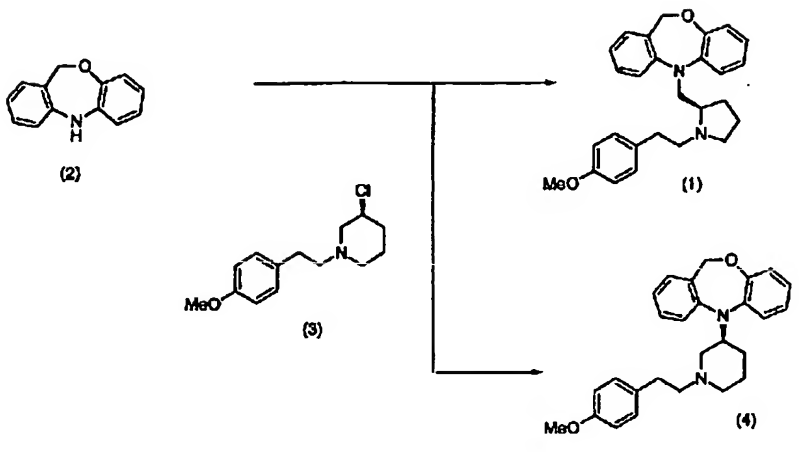

[0007]
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[0014] In addition, as mentioned above, although the researchers of this invention first tried crystallization of [b, e], and (R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine (1) made into the purpose using various solvents, neither of the solvents was able to deposit the crystal.
[0015] Moreover, although generation of the salt about acids other than a nitric acid, for example, an acetic acid, a formic acid, DL-tartaric acid, a maleic acid, a fumaric acid, a succinic acid, an adipic acid, p-toluenesulfonic acid, methansulfonic acid, a camphor sulfonic acid, and a sulfuric acid was tried, and all acquired the target salt, it was not able to do.
[0016]
[Example]
[0017] Next, the conditions of the liquid chromatography used for analysis are described.
Column YMC-Pack ODS-AM AM-302 4.6mmI.D.x 150mm Solvent 25mM sodium dihydrogenphosphate (a phosphoric acid adjusts to pH 5.6)
: Acetonitrile = 55:45 The rate of flow 1 mL/min The detecting method UV254nm Column temperature 25 degrees C Injection rate 10microL [0018] [An example 1] (R) - (+) -5, 11-dihydro-5-[1- (Preparation R)-(+)-5 of a (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate, 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine and 60% sodium hydride of (S) preparation of the mixture of [b, e], and -5 and 11-dihydro-5-[1-[2-(4-

methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine (4.51g) After the petroleum ether washed 113mmol(s), it suspended in dimethyl sulfoxide (250mL), 5, 11-hydrodibenzo [b, e], and [1, 4] oxazepine (20.3g, 103mmol) was added, and it agitated for 40 minutes at the room temperature under nitrogen-gas-atmosphere mind. The dimethyl sulfoxide (50mL) solution of a (S)-(+)-3-chloro-1-(4-methoxy phenethyl) piperidine (25 10.1 degrees (C 1.2, ethanol) of [alpha] D) (26.0g, 103mmol) was dropped at this solution, and it stirred at 50 degrees C for 5 hours. Reaction mixture was poured in into iced water and ethyl acetate extracted. Sequential washing of the organic layer was carried out with water and saturation brine, reduced pressure distilling off of the solvent was carried out after desiccation, and oily matter (36.2g) was obtained. By giving the obtained oily matter to a silica gel chromatography, and being eluted with the mixed solvent (4:1-2:1) of a hexane and ethyl acetate (R) - (+) -5, 11-dihydro-5-[1- [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and [b, e], and (S)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl) piperidine-3-IRU] dibenzo [1, 4] oxazepine were isolated, respectively.

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1H NMR (CDCl3) :delta 1.25 (m, 1H) 1.56-1.77 (m, 2H), 1.97 (dt, J= 3.3, 11.0Hz, 1H) 2.07 (m, 1H), 2.17 (m, 1H), 2.48-2.60 (m, 2H), 2.61-2.72 (m, 2H), 2.86 (m, 1H), 3.35 (m, 1H), 3.78 (s, 3H), 3.97 (m, 1H), 5.30 (br, 2H), 6.75-6.89 (m, 5H), 7.05-7.12 (m, 4H), 7.15 (m, 1H), 7.25-7.31(m, 2H).13C NMR (CDCl3) :delta 24.3, 30. 5, 32.6, 53.5, and 55.2, 57. 6, 59.6, 60.8, and 70.3, 113. 8, 119.6, and 120.9, 124. 1, 124.5, 124.9, 125.3, 128.7, 128.8, 129.5, 132.4, 133.2, 135.6, 148.4, 151.1, 157.9.ESI MASS m/z : (MH+) 415. [0020] [b, e], and (R)-(+)-5 in HPLC analysis of oily matter obtained above, and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] in addition, oxazepine (26.1g) The area ratio of 63.0mmol(s) and [b, e], and (S)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl) piperidine-3-IRU] dibenzo [1, 4] oxazepine was 7.3:1.

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[0022] Analysis (value R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate 1H NMR:(CDCl3) delta 1.92-2.28 (m, 4H), 2.85-3.15 (m, 4H), 3.48-3.61 (m, 2H), 3.79 (s, 3H), 3.91 (m, 1H), 4.05 (dd, J= 13.9, 8.2Hz, 1H), 4.52 (dd, J= 13.9, 5.4Hz, 1H) 5.16 (d, J= 12.4Hz, 1H), 5.30 (d, J= 12.4Hz, 1H) 6.80-6.90 (m, 5H), 6.98 (m, 1H), 7.04-7.13 (m, 4H), 7.23-7.36 (m, 2H), 11.6(brs, 1H).13C NMR (CDCl3) :delta 22.2 and 28.8, 31. 0, 50.3, 54.9, and 55.3, 57. 2, 65.8, 70.1, and 114.4, 119. 4, 119.5, 120.3, 121.8,124.0, 124.3, 127.6, 128.9, 129.7, 129.8, 130.7, 135.0, 149.3, 150.0, 158.8. [0023] HPLC analysis The performed place (R) - (+) -5, 11-dihydro-5-[1- The area ratio of [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and [b, e], and (S)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl) piperidine-3-IRU] dibenzo [1, 4] oxazepine The area ratio was 49.7:1.

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for 1 hour. Saturation brine washed the organic layer after the slice, and vacuum concentration of the organic layer was carried out so that the concentration of [b, e], and (R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine might become 4.5wt(s)%. It is 4M to this solution. The hydrogen chloride / ethyl-acetate solution (23mL, 92mmol) was dropped, and the (R)-(+)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine hydrochloride (17.8g, 83%) was obtained as a white crystal. When various analysis of the obtained crystal was performed, the spectrum was in agreement with it of WO97/33885 publication.
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[0026]
[Effect of the Invention] Make an optical activity 3-chloro-1-(4-methoxy phenethyl) piperidine react to 5, 11-hydrodibenzo [b, e], and [1, 4] oxazepine, and are obtained. Optical activity 5 made into the purpose, 11-dihydro-5-[1- Optical activity 5 which is [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and a by-product, 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [b, e] [1, From the mixture of 4] oxazepine Optical activity 5 made into the purpose, 11-dihydro-5-[1- It became possible to isolate easily [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine, without using the complicated purification approach industrially [a column chromatography etc.].

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EXAMPLE

[Example]
[0017] Next, the conditions of the liquid chromatography used for analysis are described.
Column YMC-Pack ODS-AM AM-302 4.6mmI.D.x 150mm Solvent 25mM sodium dihydrogenphosphate (a phosphoric acid adjusts to pH 5.6)
: Acetonitrile = 55:45 The rate of flow 1 mL/min The detecting method UV254nm Column temperature 25 degrees C Injection rate 10microL [0018] [An example 1] (R) - (+) -5, 11-dihydro-5-[1- (Preparation R)-(+)-5 of a (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine nitrate, 11-dihydro-5-[1-(4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [b, e] [1, 4] oxazepine and 60% sodium hydride of (S) preparation of the mixture of [b, e], and -5 and 11-dihydro-5-[1-[2-(4-methoxypheny) ethyl] piperidine-3-IRU] dibenzo [1, 4] oxazepine (4.51g) After the petroleum ether washed 113mmol(s), it suspended in dimethyl sulfoxide (250mL), 5, 11-hydrodibenzo [b, e], and [1, 4] oxazepine (20.3g, 103mmol) was added, and it agitated for 40 minutes at the room temperature under nitrogen-gas-atmosphere mind. The dimethyl sulfoxide (50mL) solution of a (S)-(+)-3-chloro-1-(4-methoxy phenethyl) piperidine (25 10.1 degrees (C 1.2, ethanol) of [alpha] D) (26.0g, 103mmol) was dropped at this solution, and it stirred at 50 degrees C for 5 hours. Reaction mixture was poured in into iced water and ethyl acetate extracted. Sequential washing of the organic layer was carried out with water and saturation brine, reduced pressure distilling off of the solvent was carried out after desiccation, and oily matter (36.2g) was obtained. By giving the obtained oily matter to a silica gel chromatography, and being eluted with the mixed solvent (4:1-2:1) of a hexane and ethyl acetate (R) - (+) -5, 11-dihydro-5-[1- [b, e], and (4-methoxy phenethyl)-2-pyrrolidinyl methyl] dibenzo [1, 4] oxazepine and [b, e], and (S)-5 and 11-dihydro-5-[1-(4-methoxy phenethyl) piperidine-3-IRU] dibenzo [1, 4] oxazepine were isolated, respectively.
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(51)Int.Cl.'	識別記号	ＦＩ	ﾃｰﾏｺｰﾄﾞ(参考)
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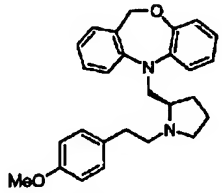
Ｆターム(参考)　4C063 AA01 BB02 CC57 DD03 EE01

(54)【発明の名称】　新規オキサゼピン誘導体結晶

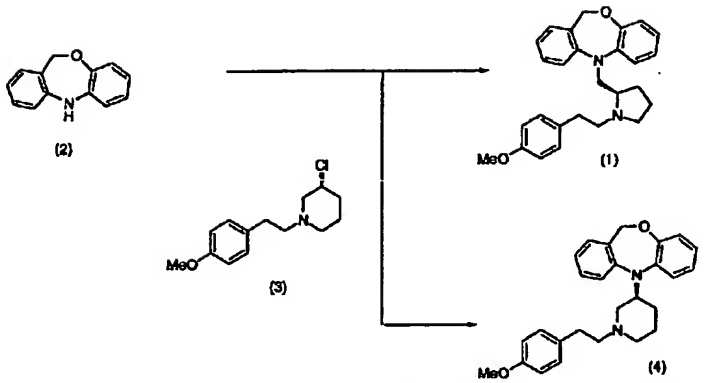
(57)【要約】
【課題】　光学活性な５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピンの工業的に有用な製造方法を確立する。
【解決手段】　光学活性な５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン及び光学活性な５，１１－ジヒドロ－５－〔１－〔２－（４－メトキシフェニル）エチル〕ピペリジン－３－イル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピンの混合物を溶剤に溶解後、硝酸を添加して析出する結晶を分離する。

【特許請求の範囲】
【請求項1】 5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩。
【請求項2】 ピロリジンの2位がR体である請求項1記載のオキサゼピン硝酸塩。
【請求項3】 5，11－ジヒドロジベンゾ〔b，e〕〔1，4〕オキサゼピン及び光学活性な3－クロロ－1－（4－メトキシフェネチル）ピペリジンを反応させて得られる光学活性な5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンと5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの混合物に溶剤を加え、硝酸を添加し、5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩を晶析し、分離する事を特徴とする5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの精製方法。
【請求項4】 光学活性な3－クロロ－1－（4－メトキシフェネチル）ピペリジンがS体であり、反応で得られる光学活性な5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン及び光学活性な5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンが（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン及び（S）－5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンであり、晶析する硝酸塩が、（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩である請求項3記載の精製方法。
【0001】
【発明の詳細な説明】
【0002】
【発明の属する技術分野】本発明は、カルシウムチャネル拮抗作用を有し、消化管運動機能異常症、特に過敏性腸症候群等の腸疾患の治療又は予防処置に有用な5，11－ジヒドロジベンゾ〔b，e〕〔1，4〕オキサゼピン誘導体の製造方法、更に詳しくは5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの精製方法に関する。
【0003】
【従来の技術】下記式（1）で示される（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンはカルシウムチャネル拮抗作用を有し、消化管運動機能異常症、特に過敏性腸症候群等の腸疾患治療又は予防処置に有用であることが知られている（WO97／33885）。
【0004】
【化1】



(1)

【0005】上記公報には（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン（1）の合成方法として下記のルートが示されているが、原料の5，11－ジヒドロジベンゾ〔b，e〕〔1，4〕オキサゼピン（2）に（S）－（+）－3－クロロ－1－（4－メトキシフェネチル）ピペリジン（3）を反応させた際に、目的とする式（1）の化合物以外に、副生成物である（S）－5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン（4）が大量に生成してしまい、目的とする化合物を得るためにはカラムクロマトグラフィー等の工業的に煩雑な精製方法を用いる必要があった。
【0006】
【化2】



【0007】
【発明が解決しようとする課題】5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの、工業的に有用な製造方法を確立することである。
【0008】
【課題を解決するための手段】本発明者らは上記の問題点を解決すべく鋭意検討を行った結果、5，11－ジヒドロジベンゾ〔b，e〕〔1，4〕オキサゼピン（2）及び光学活性な3－クロロ－1－（4－メトキシフェネチル）ピペリジン、例えば（S）－（+）－3－クロロ－1－（4－メトキシフェネチル）ピペリジン（3）の反応液を有機溶剤で抽出濃縮して得られるオイル状の残さに、溶剤を添加してこれを再溶解し、さらに硝酸を添加することにより析出する結晶を沪過、乾燥することにより目的とする、5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの硝酸塩が得られることを見いだし本発明を完成するに至った。
【0009】すなわち本発明は、5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩、特に（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩である。
【0010】また、本発明は5，11－ジヒドロジベンゾ〔b，e〕〔1，4〕オキサゼピン（2）及び光学活性な3－クロロ－1－（4－メトキシフェネチル）ピペリジンを反応させて得られる光学活性な5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンと5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの混合物に溶剤を加え、硝酸を添加し、5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩を晶析し、分離する事を特徴とする5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの精製方法。特に光学活性な3－クロロ－1－（4－メトキシフェネチル）ピペリジンがS体であり、反応で得られる光学活性な5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン及び光学活性な5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンが、（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン及び（S）－5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンであり、晶析する硝酸塩が（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩である精製方法である。
【0011】
【発明の実施の形態】本発明に於ける、5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン、特に（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン（1）と5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン、特に（S）－5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン（4）の混合物は、WO97／33885に記載の方法で製造することができる。通常、目的とする化合物（1）と副生成物である化合物（4）の比率は6：1～8：1である。
【0012】目的とする硝酸塩を得るには、上記の方法で得られた反応液に酢酸エチル、トルエン、ジクロロメタン、酢酸イソプロピル等の抽出溶剤を加え、水、飽和

食塩水等で洗浄後、必要に応じて無水硫酸ナトリウムで乾燥し、濃縮する事により光学活性な5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン及び光学活性な5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの混合物をオイル状の残さとして得ることができる。この混合物から目的とする光学活性な5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンを単独で晶析分離することが不可能であるので、次の操作により精製を行う。すなわち、上記で得られたオイル状の残さに、メタノール、エタノール、2－プロパノール、アセトニトリル、アセトン等の溶媒を添加しオイル状残さを溶解させる。溶解時の濃度は温度にもよるが20～25℃で行う場合0．1～30wt%、好ましくは1～10wt%、特に好ましくは3～5wt%が良い。この溶液に硝酸を加えることにより目的とする硝酸塩を析出させるが、硝酸を加える温度は、用いる溶剤の沸点にもよるが20～60℃、好ましくは30～50℃でおこなうと良い。また、加える硝酸の濃度は0．25～1規定、好ましくは0．4～0．6規定である。硝酸を加えた後、室温（20～25℃）で6時間から24時間放置することにより、目的とする結晶を得ることができる。この場合、撹拌等を行ってもなんら差し支えない。析出した結晶は、通常の分離方法、例えば沪過や振り切り等で行うことにより目的の結晶を単離する事ができる。通常、晶析に用いた溶剤と水の混合溶剤で洗浄することにより、目的の化合物の純度を上げることができる。さらに、この結晶を乾燥する事により、目的の硝酸塩を得ることができる。

【0013】得られた硝酸塩は、酢酸エチル等の抽出溶剤に懸濁し、水酸化ナトリウム水溶液等のアルカリ水溶液で中和、分層後、有機層を飽和食塩水で洗浄し、必要に応じて濃縮し、これに塩化水素/酢酸エチル溶液等を滴下することにより、実際に用いる5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン塩酸塩を得ることができる。

【0014】なお、上記のように本発明の研究者らはまず始めに、目的とする（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン（1）の結晶化を各種溶媒を用いて試みたが、いずれの溶媒でも結晶を析出することはできなかった。

【0015】また、硝酸以外の酸、例えば酢酸、ギ酸、DL－酒石酸、マレイン酸、フマル酸、コハク酸、アジピン酸、p－トルエンスルホン酸、メタンスルホン酸、カンファースルホン酸、硫酸についての塩の生成を試みたが、いずれも目的とする塩を取得するができなかった。

【0016】

【実施例】

【0017】次に、分析に用いた液体クロマトグラフィーの条件を記す。

カラム　YMC－Pack ODS－AM AM－302
4．6mmI．D．x 150mm
溶媒　25mMリン酸二水素ナトリウム（リン酸でpH 5．6に調整
）
：アセトニトリル ＝ 55：45
流速　1mL／min
検出法　UV254nm
カラム温度　25℃
注入量　10μL

【0018】［実施例1］（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩の調製

（R）－（+）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンと（S）－5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの混合物の調製

60%水素化ナトリウム（4．51g、113mmol）を石油エーテルで洗浄した後、ジメチルスルホキシド（250mL）に懸濁し、5，11－ジヒドロジベンゾ〔b，e〕〔1，4〕オキサゼピン（20．3g、103mmol）を加え、窒素雰囲気下、室温で40分間撹拌した。この溶液に（S）－（+）－3－クロロ－1－（4－メトキシフェネチル）ピペリジン（〔α〕D25 10．1°（C 1．2、エタノール））（26．0g、103mmol）のジメチルスルホキシド（50mL）溶液を滴下して50℃で5時間撹拌した。反応液を氷水中に注入し、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、乾燥後、溶媒を減圧留去して、油状物（36．2g）を得た。得られた油状物をシリカゲルクロマトグラフィーに付し、ヘキサンと酢酸エチルの混合溶媒（4：1～2：1）で溶出する事により、（R）－（+）－5，11－ジヒドロ－5－〔1－

（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピンと（Ｓ）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）ピペリジン－３－イル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピンをそれぞれ単離した。

【００１９】分析値

（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピンスペクトルはＷＯ９７／３３８８５に記載されている標品のそれに一致した。（Ｓ）－５，１１－ジヒドロ－５－〔１－〔２－（４－メトキシフェニル）エチル〕ピペリジン－３－イル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン（ピペリジン型副生成物）

1H NMR (CDCl3) : δ 1.25(m,1H), 1.56-1.77(m,2H), 1.97(dt,J=3.3,11.0Hz,1H),2.07(m,1H), 2.17(m,1H), 2.48-2.60(m,2H), 2.61-2.72(m,2H), 2.86(m,1H),3.35(m,1H), 3.78(s,3H), 3.97(m,1H), 5.30(br,2H), 6.75-6.89(m,5H), 7.05-7.12(m,4H), 7.15(m,1H), 7.25-7.31(m,2H).

13C NMR (CDCl3) : δ 24.3, 30.5, 32.6, 53.5, 55.2, 57.6, 59.6, 60.8, 70.3, 113.8, 119.6, 120.9, 124.1, 124.5, 124.9, 125.3, 128.7, 128.8, 129.5, 132.4, 133.2, 135.6, 148.4, 151.1, 157.9.

ESI MASS m/z : (MH+) 415.

【００２０】なお、上記で得た油状物のＨＰＬＣ分析における（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン（２６．１ｇ、６３．０ｍｍｏｌ）と（Ｓ）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）ピペリジン－３－イル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピンのエリア比率は、７．３：１であった。

【００２１】混合物からの（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン硝酸塩の調製

（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン（２６．１ｇ、６３．０ｍｍｏｌ）を含む油状物（３６．２ｇ）をエタノール（７２０ｍＬ）に溶解し、０．５Ｍ硝酸（７２０ｍＬ、３６０ｍｍｏｌ）を加えて室温で終夜で撹拌した。析出した結晶を沪過して（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン硝酸塩（２２ｇ、４３．７％）を得た。

【００２２】分析値

（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン硝酸塩

1H NMR (CDCl3) : δ 1.92-2.28(m,4H), 2.85-3.15(m,4H), 3.48-3.61(m,2H), 3.79(s,3H), 3.91(m,1H), 4.05(dd,J=13.9,8.2Hz,1H), 4.52(dd,J=13.9,5.4Hz,1H), 5.16(d,J=12.4Hz,1H), 5.30(d,J=12.4Hz,1H),6.80-6.90(m,5H), 6.98(m,1H),7.04-7.13(m,4H), 7.23-7.36(m,2H), 11.6(brs,1H).

13C NMR (CDCl3) : δ 22.2, 28.8, 31.0, 50.3, 54.9, 55.3, 57.2, 65.8, 70.1, 114.4, 119.4, 119.5, 120.3, 121.8, 124.0, 124.3, 127.6, 128.9, 129.7, 129.8, 130.7, 135.0, 149.3, 150.0, 158.8.

【００２３】ＨＰＬＣ分析を行ったところ（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピンと（Ｓ）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）ピペリジン－３－イル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピンのエリア比率は、エリア比率は、４９．７：１であった。

【００２４】［参考例１］（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン硝酸塩からの（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン塩酸塩の調製

（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン硝酸塩（２２ｇ、４４．７ｍｍｏｌ）を酢酸エチル（１０００ｍＬ）に懸濁し、０．２Ｍ　水酸化ナトリウム水溶液（５００ｍＬ、１００ｍｍｏｌ）を加えて室温で１時間撹拌した。分層後、有機層を飽和食塩水で洗浄し、（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピンの濃度が４．５ｗｔ％になるように有機層を減圧濃縮した。この溶液に４Ｍ　塩化水素／酢酸エチル溶液（２３ｍＬ、９２ｍｍｏｌ）を滴下して、（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン塩酸塩（１７．８ｇ、８３％）を白色結晶として得た。得られた結晶の各種分析を行ったところ、そのスペクトルはＷＯ９７／３３８８５記載のそれと一致した。

【００２５】［参考例２］（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２－ピロリジニルメチル〕ジベンゾ〔ｂ，ｅ〕〔１，４〕オキサゼピン塩酸塩からの（Ｒ）－（＋）－５，１１－ジヒドロ－５－〔１－（４－メトキシフェネチル）－２

－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩の調製

（R）－（＋）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン塩酸塩（1．41g、3．13mmol）をエタノール（23mL）に溶解し、0．14M 硝酸（47mL、6．5mmol）を滴下して室温で終夜で撹拌した。析出した結晶を沪過して（R）－（＋）－5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン硝酸塩（1．58g、86．4%）を得た。

【0026】

【発明の効果】5，11－ジヒドロジベンゾ〔b，e〕〔1，4〕オキサゼピンに光学活性な3－クロロ－1－（4－メトキシフェネチル）ピペリジンを反応させて得られる、目的とする光学活性な5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピン及び副生成物である光学活性な5，11－ジヒドロ－5－〔1－〔2－（4－メトキシフェニル）エチル〕ピペリジン－3－イル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンの混合物から、目的とする光学活性な5，11－ジヒドロ－5－〔1－（4－メトキシフェネチル）－2－ピロリジニルメチル〕ジベンゾ〔b，e〕〔1，4〕オキサゼピンをカラムクロマトグラフィー等の工業的に煩雑な精製方法を用いることなく容易に単離する事が可能となった。